

### **REMARKS**

Claims 1-21, 26-29 and 31-49 stand cancelled as being drawn to non-elected subject matter. Claims 22-25 and 30 are pending examination. No new claim amendments are presented at this time. Rather, reconsideration of the application is requested in view of the following remarks.

#### **Claim Rejections - 35 USC § 102**

Claims 22-25 and 30 stand rejected under 35 USC §102(b) over Dekker et al. (*Organometallics*, 3(9), pp. 1403-1407, 1984). The Office Action alleges that Dekker et al. disclose the ethyl ester of bromoacetic acid in dimeric form. The Office Action specifically points to Dekker's abstract on page 1403, Table II in the second column of 1404, and the "Discussion" on page 1406 in column 1 and column 2, as well as equilibria (2) on line 3.

The rejection is respectfully traversed. The cited document does not teach or suggest the features of the present invention. As such, it is insufficient to sustain the rejection.

Applicant disagrees with the position taken and submits that Dekker et al. ***did not obtain a crystal*** of  $(\text{BrZnCH}_2\text{COOC}_2\text{H}_5 \cdot \text{THF})_2$ .

As an initial matter, it is noted that the term "bromoacetic acid" is stated in the Office Action at page 3, 5<sup>th</sup> line from the bottom, and at page 6, 8<sup>th</sup> line. Applicant believe the term was intended to be read as –bromozincacetic acid--.

First, the Office Action asserts at page 4, 2<sup>nd</sup> line from the bottom "...the reagents (i.e., the ethyl reagent) are formed and isolated in solid form."

Reference is made to Dekker et al. at page 1404, column 1, "Preparation of the Reagent". Applicant acknowledges that a tert-butyl reagent and an ethyl reagent were obtained in solid forms.

However, for the ethyl reagent, Dekker et al. states: "For the ethyl reagent this [Applicant's notation: isolation] was done by evaporation of the solvent (yield 75%)" (Emphasis added). On the other hand, for the tert-butyl agent, Dekker et al. states "tert-butyl reagent was isolated by concentrating the supernatant liquid, after which [Applicant's notation: isolation] the reagent crystallized" (Emphasis added).

Accordingly, Dekker et al. obtained the ethyl reagent as a solvent-free solid isolation but **not as a crystal**. Whereas Dekker et al obtained the tert-butyl reagent as a crystal. This demonstrates that among the solid form of reagents, only the tert-butyl reagent could be obtained in a crystalline form and the ethyl reagent could not be crystallized.

Second, the Office Action goes on to allege at page 4, bottom line, to page 5: "On page 1404 in column 2, the last sentence before "Results", Dekker et al. disclose the reference, instrumentation, and program used for crystal structure determination."

Applicant submits that it is amply clear that the description of Dekker et al. on page 1404 in column 2 refers only to crystals of the tert-butyl reagent as the title of that section is "Data Collection and Structure Determination of (BrZnCH<sub>2</sub>COOt-bu·THF)<sub>2</sub>."

Third, the Office Action further asserts at page 5, line 3, to page 6, line 8: "On page 1404 in column 3, under "Results", Dekker et al. states...[that they] have employed molecular weight measurements to determine the degree of association of the Reformatsky reagents derived from both the ethyl and the tert-butyl ester of bromoacetic acid." The Office action contends that "hence, Dekker et al. disclose the ethyl ester of bromoacetic acid in dimeric form."

Applicant acknowledges that Dekker et al. discloses a reagent of ethyl ester of bromozincacetic acid in dimeric form. However, Applicant asserts that Dekker et al. **did not obtain any crystal** of (BrZnCH<sub>2</sub>COOC<sub>2</sub>H<sub>5</sub>·THF)<sub>2</sub>, as discussed above.

Additionally, Dekker et al. stated in a previous journal article (*J. Chem. Soc., Chem. Commun.* (1983) pages 553-555; copy attached) which was published prior to the publication date of the cited document and related to the same two Reformatsky reagents: "In our exploration of organozinc co-ordination chemistry, we have been studying the classical Reformatsky reagent (1) derived from  $\text{BrCH}_2\text{CO}_2\text{Et}$ . Since no single crystals of this species could be obtained, this study had to be confined to the characterization of the species in solution." See page 554, column 1 (emphasis added). This supports Applicant's position that Dekker et al. has not obtained crystals of  $(\text{BrZnCH}_2\text{COOC}_2\text{H}_5 \cdot \text{THF})_2$ .

In sum, Dekker's ethyl reagent did not crystallize and Dekker et al. was not able to obtain crystals of ethyl bromozincacetate according to the present invention. Only the tert-butyl reagent could be obtained in a crystalline form.

Indeed, the cited reference fails to teach or suggest the features of the claimed invention. Consequently, Dekker et al. does not anticipate the present invention. Therefore, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 22-25 and 30 under 35 USC §102(b) over Dekker et al.

In view of the foregoing, Applicant believes the pending application is in condition for allowance.

**PETITION FOR EXTENSION AND FEE AUTHORIZATION**

Applicant requests a one month extension of time for filing the within response. The Commissioner is hereby authorized to charge the fee for the extension and any other fees due or asserted to be due with this response to Deposit Account No. 04-1105.

Dated: December 19, 2008

Respectfully submitted,

Electronic signature: /Nicholas J. DiCeglie, Jr./  
Nicholas J. DiCeglie, Jr.

Registration No.: 51,615  
Christine C. O'Day

Registration No.: 38,256  
EDWARDS ANGELL PALMER & DODGE LLP  
P.O. Box 55874  
Boston, Massachusetts 02205  
(617) 517-5558  
Attorneys/Agents For Applicant

# **Exhibit**

## The Structure of the Reformatsky Reagent

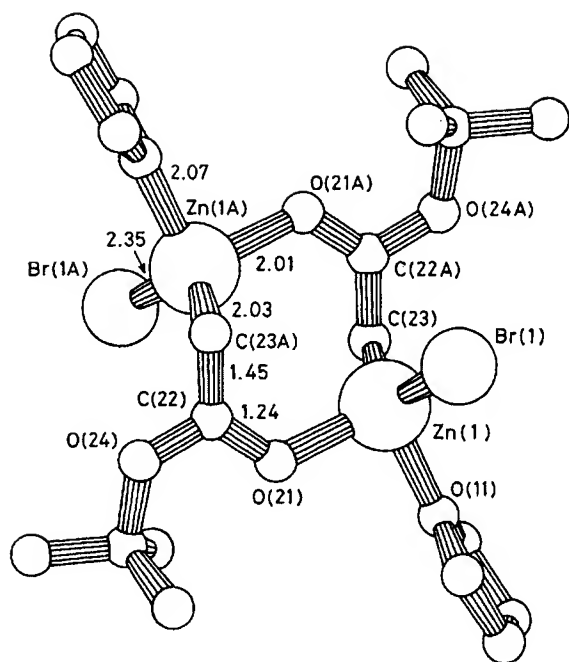
Jan Dekker, Jaap Boersma,\* and Gerrit J. M. van der Kerk

*Laboratory for Organic Chemistry, State University, Croesestraat 79, 3522 AD Utrecht, The Netherlands*

The Reformatsky reagent ' $\text{BrZnCH}_2\text{CO}_2\text{R}$ ' is a cyclic dimer with bridging  $-\text{CH}_2\text{C}(\text{OR})\text{O}-$  groups.

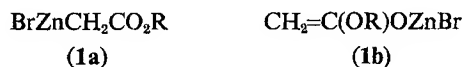
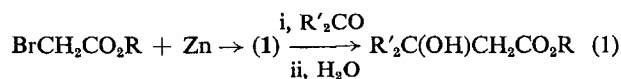
The Reformatsky reaction (1) has been used in synthetic organic chemistry for almost a century. Although various preparative aspects of this reaction have been explored

extensively,<sup>1</sup> only little is known about the true nature of the intermediate (1), the Reformatsky reagent. Both *C*-metallated (1a) and *O*-metallated (1b) species have been proposed on the



**Figure 1.** Crystal structure of  $(\text{BrZnCH}_2\text{CO}_2\text{Bu}^t\cdot\text{THF})_2$ , with bond lengths in Å, showing the crystallographic numbering system; bond angles are  $\text{O}(21)\text{--C}(22)\text{--C}(23\text{A})$ ,  $124.8^\circ$ ;  $\text{C}(22)\text{--C}(23\text{A})\text{--Zn}$ ,  $108.9^\circ$ ;  $\text{C}(23\text{A})\text{--Zn--O}(21\text{A})$ ,  $111.0^\circ$ ;  $\text{Zn--O}(21\text{A})\text{--C}(22\text{A})$ ,  $125.5^\circ$ .

basis of spectroscopic data.<sup>2-4</sup> However, no molecular structures, either in solution or in the solid state, have been established.

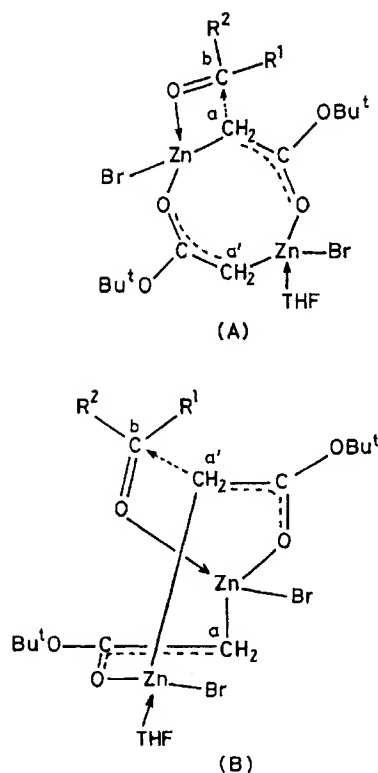


In our exploration of organozinc co-ordination chemistry, we have been studying the classical Reformatsky reagent (1) derived from  $\text{BrCH}_2\text{CO}_2\text{Et}$ . Since no single crystals of this species could be obtained, this study had to be confined to the characterization of the species in solution. Recently Orsini *et al.*<sup>4</sup> reported that the Reformatsky reagent prepared from zinc and  $\text{BrCH}_2\text{CO}_2\text{Bu}^t$  in tetrahydrofuran (THF) was a microcrystalline compound. We have grown single crystals of this compound and determined its structure by X-ray diffraction analysis.

**Crystal data:** monoclinic, space group  $P2_1/n$ ,  $a = 10.322$ ,  $b = 12.357$ ,  $c = 11.654$  Å,  $\beta = 112.65^\circ$ ,  $Z = 2$  (dimeric units). The refinement, based on a partial data set (1133 reflections), converged at an  $R$  value of 0.073.

The zinc is almost tetrahedrally surrounded by two oxygen, one bromine, and one carbon atom. The dimeric unit forms an 8-membered non-planar ring,  $(\text{ZnCCO})_2$ , with normal zinc-carbon and zinc-oxygen single bond distances. This unit is depicted in Figure 1, with bond lengths and angles indicated.

† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.



**Figure 2.** Proposed intermediates in the reaction of the Reformatsky reagent with a ketone. (A) Four-centre mechanism (attack of  $\text{C}^a$  on  $\text{C}^b$ ). (B) Six-centre mechanism (attack of  $\text{C}^{a'}$  on  $\text{C}^b$ ).

A comparable 8-membered ring,  $(\text{ZnNCO})_2$ , was found some years ago in the structure of methyl *N*-phenyl-*N*-ethylzinciocarbamate.<sup>5</sup>

Ebulliometry in THF showed that the *t*-butyl compound retains its dimeric structure in this solvent. The corresponding reagent derived from  $\text{BrCH}_2\text{CO}_2\text{Et}$  is also a dimer in THF, dioxan, and pyridine. Moreover, the n.m.r. spectra of both reagents in THF,  $\text{Me}_2\text{SO}$ , and pyridine show in each case almost identical chemical shifts for the  $\text{CH}_2$  group bound to zinc. We therefore believe that this dimeric structure is the basic structure of the Reformatsky reagent. For this reason it is, in our opinion, incorrect to describe the reagent as either a *C*-metallated<sup>4</sup> or an *O*-metallated<sup>2</sup> mononuclear species.

Any mechanism operative in the Reformatsky reaction (1) must take into account the dimeric structure of the reagent. The first step will undoubtedly be the displacement of a co-ordinated solvent molecule by a carbonyl compound. In the second step the carbonyl group can react either with the  $\text{CH}_2$  group of the zinc atom to which it is co-ordinated in a four-centre mechanism (Figure 2A), or with the  $\text{CH}_2$  group attached to the other zinc atom of the dimer in a six-centre mechanism (Figure 2B). The first possibility is analogous to the mechanism proposed by Ashby and Bowers<sup>6</sup> for the formation of the 1,2-addition product in the reaction of Grignard reagents with benzophenone. The second one resembles the mechanism for the Reformatsky reaction proposed by Mousseron *et al.*<sup>7</sup>

A model study shows that more steric hindrance occurs between the carbonyl compound and the dimeric reagent in the four-centre mechanism than in the six-centre mechanism. Moreover, in the six-centre mechanism the carbonyl group can more easily approach the carbon atom to which it is going to be attached. On the basis of these considerations, we prefer the six-centre mechanism.

We are grateful to Dr. A. L. Spek and Mr. A. J. M. Duisenberg for the collection of the X-ray data.

Received, 20th January 1983; Com. 094

### References

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